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Original article

Impairment of platelet retention rate in patients with severe aortic valve stenosis

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ABSTRACT

Background: Recent reports revealed the presence of acquired von Willebrand syndrome type 2A in patients with aortic valve stenosis (AS). von Willebrand factor (vWF) has been shown to play a vital role in platelet adhesion. Therefore, we measured the platelet retention rates, which reflect platelet adhesion, in patients with severe AS.

Methods: In addition to echocardiography, routine blood screening tests were performed and the platelet retention rates were measured using collagen-coated bead columns in 21 patients with severe AS and in 21 control subjects.

Results: Patients with severe AS showed the maximum aortic valve pressure gradients of 110.9 ± 22.7 mmHg, and effective orifice areas of 0.59 ± 0.20 cm^2. The results of routine blood tests in patients with severe AS were comparable to those of control subjects; however, the platelet retention rates in the AS patients ($7.3 \pm 5.0\%$) were significantly lower than those in control subjects ($30.5 \pm 11.8\%$, $p < 0.001$). A significant negative correlation was observed between maximum aortic valve pressure gradients and platelet retention rates ($r = -0.81$, $p < 0.001$). In 8 patients with severe AS, the platelet retention rates increased from $5.8 \pm 3.6\%$ to $16.0 \pm 2.4\%$ after aortic valve replacement ($p < 0.001$).

Conclusion: These findings suggest that impairment of platelet retention rate is seen in almost all patients with severe AS. Clinicians should be aware of the possibilities of vWF-mediated platelet dysfunction and bleeding tendency in patients with severe AS.

Introduction

Sclerosis, calcification, and stenosis of the aortic valve are the most common acquired valvular lesions in elderly patients. Increased life expectancy has resulted in an increase in the population of elderly people, with a corresponding increase in the number of patients with such degenerative aortic valve diseases. Otto et al. reported that 29% of individuals older than 65 years have aortic valve sclerosis, and 2% of this population has aortic valve stenosis (AS) [1]. The rate of AS progression may be more rapid in elderly patients [2], and some reports demonstrate that hemodialysis, serum calcium, hypertension, and hyperlipidemia among other things are associated with the progression of AS [3,4].

In 1958, Heyde first reported that 10 patients with AS had gastrointestinal bleeding of unknown cause [5]. In the same year, Goldman reviewed 37,423 patients and showed a 3-fold higher incidence of gastrointestinal bleeding than the predicted incidence in patients with AS [6]. The precise mechanism underlying the link between AS and gastrointestinal bleeding tendency was unknown for a long time. Vincentelli et al. demonstrated that the high-molecular-weight von Willebrand multimers were reduced in proportion to the severity of AS, and valve replacement could restore the impaired distribution of the multimers [7]. Nowadays, the relationship between AS, acquired von Willebrand syndrome type 2A (deficiency in high-molecular-weight von Willebrand multimers), and anemia due to gastrointestinal bleeding from intestinal angiodysplasia is known as Heyde syndrome [8]. However, patients with severe AS usually have normal results in routine blood screening tests. Therefore, many clinicians are probably unaware of the abnormal hemostasis in patients with severe AS.

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The interaction between von Willebrand factor (vWF) and platelet glycoprotein (GP) Ib plays a critical role in the initial phase of platelet adhesion, particularly under high shear stress [9]. Until recently, quantification of platelet adhesiveness was performed using glass-bead columns, and the methods for quantitative estimation were developed and modified [10]. The methods principally measured the retention of platelets during passage of whole blood through glass-bead columns. Now, spherical copolymer plastic beads coated with porcine type I collagen have been developed and are being used for the measurement of platelet retention [11]. Because collagen is a major subendothelial component, measurement of platelet adhesion using this assay is expected to reflect physiologic platelet responses more accurately than the glass-bead columns. vWF might affect the platelet retention rates measured using the collagen-coated bead columns. Ideguchi et al. reported that 62% of platelet adhesion to the collagen-coated bead columns was inhibited by the antibody of vWF (MAS534p), which inhibits GPIb binding site of vWF [12]. We previously reported a patient with Heyde syndrome who showed normal results of almost all routine blood screening tests, but a significant decrease in the platelet retention rate measured using this collagen-coated bead column method and the deficiency in high-molecular-weight von Willebrand multimers by gel electrophoresis [13].

Thus, in this study, we examined whether the platelet retention rates in patients with severe AS are lower than those in control subjects and whether platelet retention rates change after aortic valve replacement (AVR). Additionally, we evaluated the relationship between platelet retention rate and aortic valve pressure gradient as an indicator of shear stress.

Methods

Study patients

Between August 2009 and December 2012, 21 consecutive patients (8 men and 13 women; mean ± SD age, 75.2 ± 10.2 years) referred to Shimane University Hospital for evaluation of severe AS were enrolled in the study.

The diagnosis of severity was made according to the European Association of Echocardiography/American Society of Echocardiography guidelines [14]. Thus, severe AS was defined as an aortic valve area less than 1.0/cm^2 or a mean gradient greater than 40 mmHg, as determined by Doppler echocardiography.

In addition, 21 control subjects who visited our hospital for further medical examination of hypertension and electrocardiogram abnormalities (12 men and 9 women; mean ± SD age, 69.0 ± 8.6 years) were enrolled in the study.

The exclusion criteria were personal or family history of genetic bleeding disorder or thrombotic disorder, platelet counts <100,000 or >450,000 mm^{-3}, serum creatinine levels >2.0 mg/dl, acute infectious disease, autoimmune disorders, neoplasm, viral hepatitis, or significant valve diseases other than AS. Further, patients receiving any antiplatelet or anticoagulant treatment and steroids or nonsteroidal anti-inflammatory drugs at the time of evaluation were excluded from the present study.

Baseline characteristics of patients with severe AS and control subjects are shown in Table 1. Patients with severe AS (75.2 ± 10.2 years) were significantly older than control subjects (69.0 ± 8.6 years, $p = 0.037$). There were no significant differences between the groups regarding the prevalence of diabetes mellitus and hyperlipidemia, and the administration of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and statins. The numbers of patients with hypertension and receiving administration of a Ca antagonist were much higher among the control subjects ($p = 0.012$, 0.015, respectively).

Written informed consent was obtained from each patient and control subjects.

Echocardiographic evaluation

Transthoracic echocardiography was performed using a Philips iE33 echocardiographic system (Andover, MA, USA) to assess the hemodynamic performance of the aortic valve in patients with severe AS and in control subjects on the same day or within a few days of the platelet retention tests. The mean and peak transvalvular pressure gradients were calculated using the modified Bernoulli equation, and the effective orifice area was calculated using the continuity equation [15].

Blood collection and laboratory assays

Blood samples were collected for simultaneous assessment of platelet retention rates, platelet counts, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), and fibrinogen levels.

In the present study, we performed the multimers analysis of vWF by gel electrophoresis in 5 patients with severe AS. Additionally, we measured the activities of the vWF-cleaving protease ADAMTS 13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) which targets the A2 domain of vWF and specifically cleaves the protein Tyr1605-Met1606 [16], in 5 patients with severe AS.

Fasting-state blood samples were obtained from all patients with severe AS and from control subjects at 10:00 AM. Blood samples were drawn from the antecubital vein under minimal tourniquet pressure using a sterile 21-gauge needle syringe. All parameters were measured by routine laboratory techniques blinded to the origin of the sample.

Measurement of platelet retention rate

In an air conditioned room at a temperature of 25–26 °C, the platelet retention rate was measured in all patients with severe AS and in control subjects according to the methods described by Kaneko et al. [11]. Briefly, co-polymer plastic beads (diameter, 0.4–0.6 mm) coated with porcine type I collagen were packed into a polyvinyl tubing with an internal diameter of 2 mm and length of 80 mm. These Pla-Bead columns are disposable and commercially available, and they are distributed by ISK Co., Ltd., Tokyo, Japan. The whole blood samples were mixed by twirling and 1.5 ml of the sample was drawn into a plastic syringe (2.5 ml) (Terumo, Tokyo, Japan). A collagen-coated bead column was connected to the syringe, and the syringes were placed in the holder of an injection pump. The blood samples in the syringes were passed through the collagen-coated bead columns at a fixed flow rate of 1.5 ml/30 s.

Table 1
Comparison of baseline characteristics of study patients and control subjects.

	Severe AS group ($n = 21$)	Control subjects ($n = 21$)	p-Value
Age (years)	75.2 ± 10.2	69.0 ± 8.6	0.037
Sex (female/male)	13/8	9/12	0.217
Hypertension	8	16	0.013
Diabetes mellitus	3	1	0.293
Hyperlipidemia	8	8	1.000
Medication use (n)			
ACE-I/ARB	7	8	0.747
Ca-blocker	6	11	0.015
β-blocker	1	3	0.293
Statin	8	8	1.000

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. AS, aortic valve stenosis.

The samples before and after passage through the columns were collected into plastic tubes containing EDTA, and platelet counts were measured by an automated hematology analyzer, XE-2100 (Sysmex, Kobe, Japan). Platelet retention rates (%) were calculated as follows: 100[(platelet count before passage) − (platelet count after passage)]/(platelet count before passage).

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (Chicago, IL, USA). Values are expressed as the mean ± standard deviation (SD). Comparisons between the 2 groups were performed using Mann–Whitney *U* test, and Wilcoxon signed-rank test was used to compare before and after AVR. The relationship between continuous variables was examined by Spearman's rank-correlation test. A p-value < 0.05 was considered statistically significant.

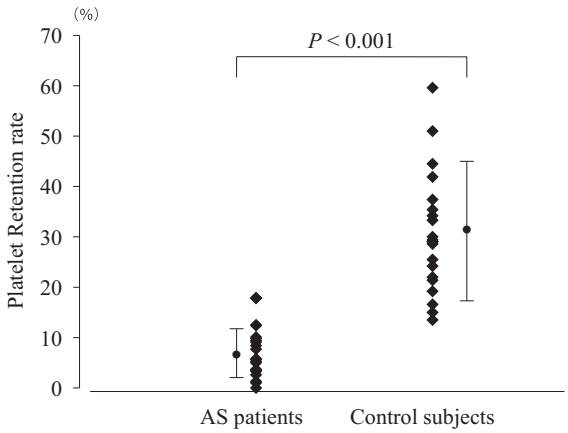

Fig. 2. The platelet retention rate in control subjects and in patients with severe aortic valve stenosis (AS).

Results

Echocardiography data and laboratory parameters of patients with severe AS and control subjects are shown in Table 2.

In patients with severe AS, the maximum aortic valve pressure gradient was 110.9 ± 22.7 mmHg, the mean aortic valve pressure gradient was 66.4 ± 15.5 mmHg, and effective orifice area calculated using the continuity equation was 0.59 ± 0.20 cm^2.

In both patients with severe AS and in control subjects, the values of the routine blood screening tests (platelet counts, PT-INR, APTT, and fibrinogen) were within normal limits, and no significant difference was observed between the 2 groups except for PT-INR.

In 5 patients with severe AS, the multimers analysis of vWF by gel electrophoresis revealed loss of the large multimers of vWF (Fig. 1). Additionally, the activities of ADAMTS 13 in all 5 of these patients were within normal limits (87.8 ± 10.1%, normal 70–120%).

The platelet retention rate varied from 13.5% to 59.6% in control subjects and the mean value was 30.5 ± 11.8%. However, the platelet retention rates in patients with severe AS (7.3 ± 5.0%) were significantly lower than those in control subjects (30.5 ± 11.8%, p < 0.001, Fig. 2). In the linear regression analysis on the correlation with the platelet retention rates and maximum aortic valve pressure gradients, we have additionally investigated 4 mild-moderate AS patients in order to increase the accuracy of our research. In the 4 patients with mild-moderate AS, the maximum aortic valve pressure gradients were 42, 43, 66, and 68 mmHg, and the platelet retention rates were 30.9%, 29.0%, 17.2%, and 15.6%, respectively. The linear regression analysis showed that the platelet retention rate had a significant and negative correlation with maximum aortic valve pressure gradient (r = −0.81, p < 0.001, Fig. 3).

Table 2
Comparison of echocardiographic and blood screening data of study patients and control subjects.

	Severe AS group(n = 21)	Control subjects(n = 21)	p-Value
Echocardiographic data			
Maximum transvalvular gradient (mmHg)	110.9 ± 22.7	9.0 ± 5.3	<0.001
Mean transvalvular gradient (mmHg)	66.4 ± 15.5	4.8 ± 3.0	<0.001
Aortic valve area (cm^2)	0.59 ± 0.20	2.68 ± 0.54	<0.001
Laboratory parameters			
Platelet counts (×10/mm^3)	20.4 ± 4.6	20.2 ± 2.7	0.819
PT-INR	0.96 ± 0.07	0.91 ± 0.06	0.013
APTT (s)	33.2 ± 4.6	30.9 ± 3.1	0.067
Fibrinogen (mg/dl)	305.7 ± 78.5	277.6 ± 47.0	0.178

AS, aortic valve stenosis; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time.

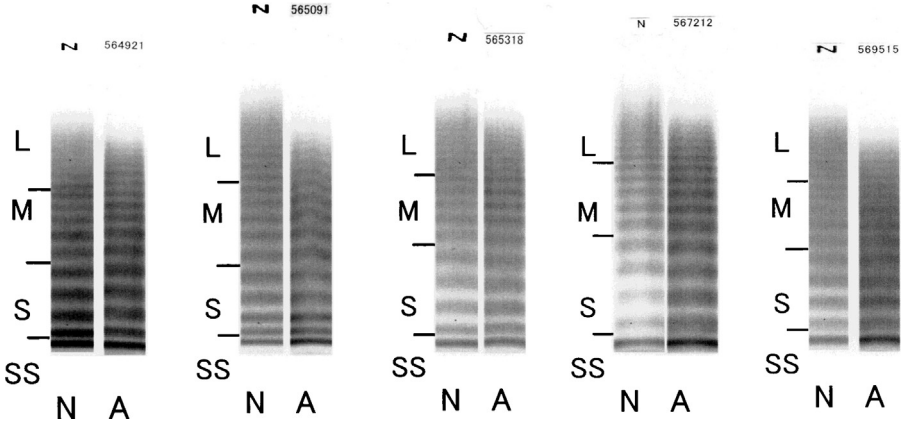

Fig. 1. The multimers analysis of von Willebrand factor by gel electrophoresis in 5 patients with severe aortic valve stenosis (AS). N, control subject; A, patient with severe AS. L, large multimer; M, middle multimer; S, small multimer; SS, very small multimer.

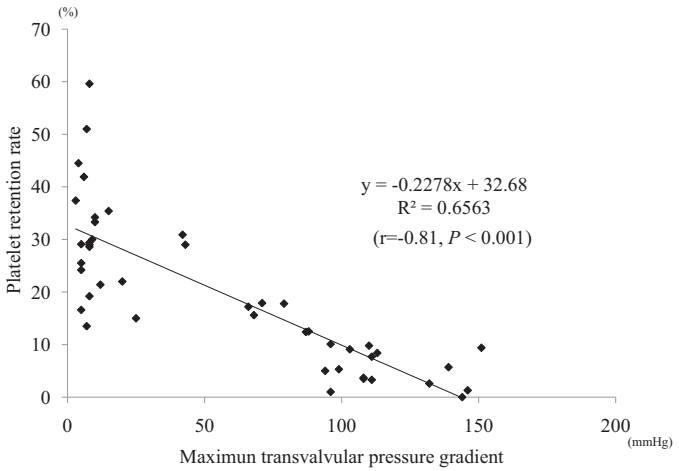

Fig. 3. Linear regression analysis on the correlation with the platelet retention rates and maximum aortic valve pressure gradient.

In this study, 2 of the 21 patients with severe AS showed gastrointestinal bleeding from angiodysplasia.

Receiver operating characteristic curves were constructed to explore the diagnostic utility of the platelet retention rate for severe AS. Estimates of the area under the curve showed the platelet retention rate to be good for detecting severe AS, with an area under the curve of 0.986. In an exploratory analysis of possible cut-off points for the platelet retention rate, a threshold of 14.3% demonstrated 95% sensitivity, and 91% specificity for the detection of severe AS.

In the present study, we had the opportunity to re-evaluate 8 patients with severe AS after they had undergone AVR. We again measured the platelet retention rate and performed echocardiography 154 ± 142 days after AVR. The maximum aortic valve pressure gradients in these patients had significantly decreased from 109.6 ± 21.9 mmHg to 50.9 ± 19.2 mmHg after AVR ($p < 0.001$), and the platelet retention rates had significantly increased from 5.8 ± 3.4% to 16.0 ± 2.4% after AVR ($p < 0.001$, Fig. 4).

Discussion

To our knowledge, this is the first report on the platelet retention rates in patients with severe AS. Although the values of routine blood screening tests in patients with severe AS were within normal limits, the platelet retention rates in these patients were significantly lower than those in control subjects. The platelet retention rate had a significant and negative correlation with maximum aortic valve pressure gradient. Additionally, platelet retention rates significantly improved after AVR.

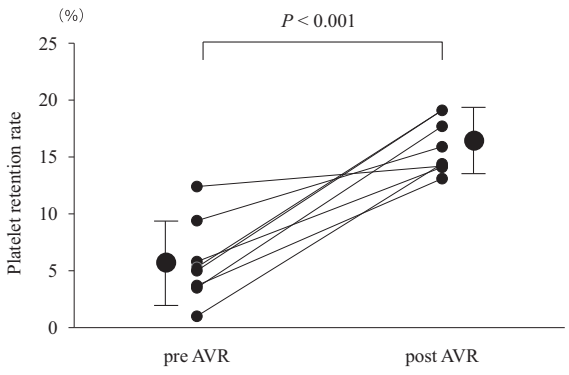

Fig. 4. The platelet retention rates before and after aortic valve replacement (AVR) in patients with severe aortic valve stenosis.

vWF is a plasma glycoprotein that mediates shear-dependent platelet adhesion to the subendothelium and the subsequent platelet-platelet interactions. vWF binds to the platelet receptor glycoprotein Ib/IX and to injured vessel walls by interacting with collagen. vWF is synthesized in endothelial cells and megakaryocytes as an ultra-large molecule. vWF multimers secreted into blood can be >20 million Da in mass and 4 μm in length. Upon secretion, molecular size of vWF is reduced by ADAMTS-13. ADAMTS-13 cleaves the Tyr1605-Met1606 peptide bond within the vWF A2 domain thus generating smaller multimers and proteolysis fragments. The larger multimers of vWF are more likely to bind to platelets and collagen, and to promote platelet adhesion in circulating blood [16].

Tsai et al. demonstrated that shear stress enhances the proteolysis of vWF multimers in normal plasma [17]. Recent experimental reports showed that high shear stress can alter the structure of the vWF molecule and induce unfolding of the A2 domain which is sensitive to the action of ADAMTS-13 [18,19]. Vincentelli et al. [7] reported that many patients with severe AS have acquired von Willebrand disease type 2A. vWF multimer is subjected to high fluid shear stress when is passes through the stenosed aortic valve and that renders the multimers susceptible to cleavage by ADAMTS-13, and loss of the largest vWF multimers leads to impairment of primary hemostasis and results in bleeding tendency. In the present study, the activities of ADAMTS 13 in all 5 severe AS patients were within normal limits. Recent reports demonstrated [18,19] that conformational change of high-molecular-weight von Willebrand multimers is induced by high shear stress, exposing sites on A2 domains that can be cleaved by ADAMTS-13. Additionally, Loscalzo reported that it was not ADAMTS-13 activity itself but the conformation of the vWF substrate that regulates its proteolysis [20]. Therefore, in the present study, these conformational mechanisms would presumably be responsible for the decrease in high-molecular-weight von Willebrand multimers in patients with severe AS.

However, in the present study, almost all patients with severe AS showed normal results of routine blood screening tests. Therefore, many clinicians are probably unaware of the abnormal hemostasis in patients with severe AS. Actually, Goldman showed a 3-fold higher incidence of gastrointestinal bleeding than the predicted incidence in patients with AS [6]. Vincentelli et al. reported that 9 (21.4%) of 42 patients with severe AS had at least one episode of abnormal bleeding, usually skin or mucosal bleeding [7]. Schodel et al. reported severe recurrent epistaxis in 2 patients with severe AS [21]. Also in our study, 2 of the 21 patients with severe AS showed gastrointestinal bleeding from angiodysplasia. Their platelet retention rates were 7.7% and 8.4%, respectively. However, in the present study, the numbers of such patients were small. Therefore, further studies are required to clarify the precise correlation between the platelet retention rate and the occurrence of bleeding events.

In 2003, Kaneko et al. demonstrated a new, simple assay for determining platelet function using a column of collagen-coated beads. The platelet retention rate in the column principally represents platelet adhesion and following aggregation at the injured artery with high reproducibility [11]. The interaction between vWF and GP Ib plays a critical role in the initial phase of platelet adhesion, particular under high shear stress [9]. Additionally, Ideguchi et al. reported that 62% of platelet adhesion to collagen-coated bead columns was inhibited by the antibody of vWF (MAS534p), which inhibits GPIb binding site of vWF [12]. Therefore, we think that impairment of platelet retention rate might reflect vWF-mediated platelet dysfunction in patients with severe AS. In the present study, we showed that the platelet retention rate had a significantly negative correlation with maximum transvalvular pressure gradient. These findings are also consistent with

Vincentelli's finding that the percentages of the highest molecular weight vWF multimers were negatively correlated with the mean transvalvular gradient in patients with severe AS. Accordingly, decrease or loss of high-molecular weight vWF multimers might induce the impairment of the platelet retention rate.

In the present study, we showed that the platelet retention rates significantly improved after AVR. Several reports showed that loss of the high molecular weight vWF multimers improve after AVR [7,22]. Recently, Thompson et al. showed that more than 75% of AS patients with gastrointestinal bleeding due to angiodysplasia have no bleeding symptom after AVR [23]. Thus, abnormal bleedings such as gastrointestinal bleeding due to angiodysplasia may be considered as an indication for AVR in patients with significant AS.

In the present study, the platelet retention rates improved after AVR, but, were not equal to those of the control subjects. We speculate that two factors might have affected this result. First, the maximum aortic valve pressure gradients did not completely normalize after AVR (decreasing from 109.6 to 50.9 mmHg), such that the residual pressure gradients might have impaired restoration of the platelet retention rates. Second, anticoagulant and/or antiplatelet agents were prescribed to 7 patients after AVR. These factors might have reduced the recoveries of platelet retention rates.

In various tests for acquired vWF deficiency, gel electrophoresis of vWF is most sensitive [8]. However, gel electrophoresis of vWF is complicated and requires cost and time. By contrast, the advantage of the collagen-coated beads column method over the other methods includes easy procedure and low cost of instruments. Measurement of the platelet retention rate using a column of collagen-coated beads might be clinically useful for monitoring the vWF-mediated platelet dysfunction in patients with severe AS.

Study limitations

Our study has several limitations. First, we enrolled a very small number of patients in this study, because of the numerous and strict exclusion criteria. Thus, this assay method should be evaluated in a larger number of patients for verification of its clinical utility.

Our data showed wide variability in the platelet retention rate in control subjects. However, the wide variability of the platelet activity is consistent with the data from the other platelet retention rate test. Cuyun-Lira et al. showed that the platelet retention rate measured using collagen-coated bead columns varied from 16% to 78% in 18 healthy individuals and the mean ± SD value was 38.7% ± 16.0% [24]. On the basis of high reproducibility of the platelet retention assay [11], the wide variability of the platelet retention rate may reflect the individual variability itself but not the methodological variability.

In the present study, the patients with severe AS were significantly older than the control subjects ($p = 0.037$). Conversely, the numbers of patients with hypertension and receiving administration of a Ca antagonist were much higher among the control subjects than the AS patients ($p = 0.012$, $p = 0.015$, respectively). However, neither age-related changes in the platelet retention rate, nor effects of hypertension and Ca antagonists on this rate have been reported to date. Further studies with a larger population of healthy individuals of various ages and patients with hypertension are required.

Additionally, we investigated only 4 mild-moderate AS patients in the present study. Therefore, further studies focusing on the mild-intermediate AS patients are required to clarify the correlation between the platelet retention rate and the severity of AS.

Conclusion

Our findings suggest that the platelet retention rate is reduced in almost all patients with severe AS. In patients with severe AS, abnormal bleedings such as gastrointestinal angiodysplasia may be not a coincidence but a consequence of the loss of the high-molecular-weight multimers of vWF in the plasma. Clinicians should be aware of the vWF-mediated platelet dysfunction and bleeding tendency in patients with severe AS.

Conflict of interest

We have no conflict of interest and no financial disclosure to declare in conjunction with the publication of this work.

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References

[1] Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
[2] Du X, Soon JL. Mild to moderate aortic stenosis and coronary bypass surgery. J Cardiol 2011;57:31–5.
[3] Hoshina M, Wada H, Sakakura K, Kubo N, Ikeda N, Sugawara Y, Yasu T, Ako J, Momomura S. Determinants of progression of aortic valve stenosis and outcome of adverse events in hemodialysis patients. J Cardiol 2012;59:78–83.
[4] Waters DD. Exploring new indications for statins beyond atherosclerosis: successes and setbacks. J Cardiol 2010;55:155–62.
[5] Heyde EC. Gastrointestinal bleeding in aortic stenosis. N Engl J Med 1958;259:196.
[6] Goldman MJ. Aortic stenosis and gastrointestinal bleeding. N Eng J Med 1958;259:941.
[7] Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, Goudemand J, Prat A, Jude B. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343–9.
[8] Massyn MW, Khan SA. Heyde syndrome: a common diagnosis in older patients with severe aortic stenosis. Age Ageing 2009;38:267–70.
[9] Berndt MC, Shen Y, Dopheide SM, Gardiner EE, Andrews RK. The vascular biology of the glycoprotein Ib-IX-V complex. Thromb Haemost 2001;86:178–88.
[10] Carr Jr ME. In vitro assessment of platelet function. Transfus Med Rev 1997;11:106–15.
[11] Kaneko M, Cuyun-Lira O, Takafuta T, Suzuki-Inoue K, Satoh K, Ohtsuki K, Ohnishi M, Arai M, Yatomi Y, Ozaki Y. Mechanisms of platelet retention in the collagen-coated-bead column. J Lab Clin Med 2003;142:258–67.
[12] Ideguchi H, Takao M, Nakamura K, Sonoda M, Kawashima H, Ono J. Determination of platelet adhesiveness to collagen-coated beads using citrated blood. Jpn J Med Pharm Sci 2000;43:801–6.
[13] Takahashi N, Tanabe K, Yoshitomi H, Sato M, Kitamura J, Sato H, Ishibashi Y, Shimada T, Oda T. Successful endoscopic clipping for bleeding from colonic angiodysplasia in a case of Heyde syndrome. Med Sci Monit 2010;16:CS107–9.
[14] Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Lung B, Otto CM, Pellikka PA, Quinones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:442–65.
[15] Teirstein P, Yeager M, Yock PG, Popp RL. Doppler echocardiographic measurement of aortic valve area in aortic stenosis: a noninvasive application of the Gorlin formula. J Am Coll Cardiol 1986;8:1059–65.
[16] Sadler JE. New concepts in von Willebrand Disease. Annu Rev Med 2005;56:173–91.
[17] Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. Blood 1994;83:2171–9.
[18] Zhang X, Halvorsen K, Zhang CZ, Wong WP, Springer TA. Mechanoenzymeatic cleavage of the ultralarge vascular protein von Willebrand factor. Science 2009;324:1330–4.
[19] Crawley JT, de Groot R, Xiang Y, Luken BM, Lane DA. Unraveling the scissile bond: how ADAMTS 13 recognizes and cleaves von Willebrand factor. Blood 2011;118:3212–21.
[20] Loscalzo J. From clinical observation to mechanism – Heyde's syndrome. N Engl J Med 2012;367:1954–6.
[21] Schodel J, Obergfell A, Maass AH. Severe aortic valve stenosis and nosebleed. Int J Cardiol 2007;120:286–7.
[22] Yoshida K, Tobe S, Kawata M. Acquired von Willebrand disease type II A in patients with aortic valve stenosis. Ann Thorac Surg 2006;81:1114–6.
[23] Thompson III JL, Schaff HV, Dearani JA, Park SJ, Sundt III TM, Suri RM, Blackshear JL, Daly RC. Risk of recurrent gastrointestinal bleeding after aortic valve replacement in patients with Heyde syndrome. J Thorac Cardiovasc Surg 2012;144:112–6.
[24] Cuyun-Lira O, Kaneko M, Takafuta T, Satoh K, Ohnishi M, Yatomi Y, Ozaki Y. Inhibitory effects of ticlopidine on platelet function as assessed by three different methods. Eur J Pharm Sci 2007;30:21–5.